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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,996	12/03/2001	William M. Partridge	407T-994110US	3004
22798	7590	10/28/2004	EXAMINER	
QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C. P O BOX 458 ALAMEDA, CA 94501			ASHEN, JON BENJAMIN	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 10/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/005,996	PARTRIDGE ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Jon B. Ashen	1635	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 5/12/04.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-61 is/are pending in the application.
- 4a) Of the above claim(s) 4,26 and 27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-25 and 28-31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>10/02;8/02;11/03</u> .  | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election of Group I, claims 1-31, in the reply filed on 5/21/04, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

### ***Status of the Application***

Claims 1-61 are pending in this application. Claims 4, 26-27 and 32-61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-3, 5-25 and 28-31 are currently under examination.

### ***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1 and 3 (and claims 2, 5-25 and 28-31, which depend directly or indirectly from claims 1 or 3) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant case, claims 1 and 3 recite, "on a cell comprising the blood brain barrier." One of skill in the art cannot determine what is meant by this claim limitation because one of skill in the art considers that the blood

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brain barrier is comprised of cells and cannot envision the metes and bounds of a claim drawn to a single cell that comprises the entire blood brain barrier. Additionally, claim 1 recites, "said gene or cDNA" at the end of the last line. In the instant case, it appears that said refers to both gene and cDNA. However, there is no antecedent basis for the limitation of "said cDNA" in this claim.

4. Claims 2 and 15 each recite the limitation "said nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 1, from which claims 2 and 15 depend, sets forth 2 distinct nucleic acids.

5. Claim 28 recites the limitation "said contacting" in line 19+. There is insufficient antecedent basis for this limitation in the claim.

### ***Claim Rejections - 35 USC § 102***

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-3, 6-16, 18-24, and 28-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Penichet et al. (1999; Reference 39, PTO-1449 filed 8/23/04, instant application). Claims 1-3, 6-16, 18-24, and 28-30 are drawn to a method of imaging in

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imaging in vivo expression of a gene in a brain cell in a vertebrate comprising a) administering an imaging reagent comprising a detectable label attached to a first nucleic acid that specifically hybridizes to a second nucleic acid transcribed from said gene where the first nucleic acid is linked to a targeting ligand that binds a receptor on a cell of the blood brain barrier and crosses said barrier and b) detecting the presence or quantity of a signal produced by the detectable label in brain cells wherein the presence or quantity of said label indicates the presence or quantity of a nucleic acid transcribed from said gene (claim 1) wherein said nucleic acid is a peptide nucleic acid (PNA) (claims 2, 9) wherein said targeting ligand is an antibody that specifically binds to a receptor on a cell of the blood brain barrier (claim 3) wherein the targeting ligand is an antibody that specifically binds to an insulin receptor (claim 5) wherein the first nucleic acid is linked to the targeting ligand by a linker or affinity tag (claim 6) wherein the affinity tag comprises a biotin and a molecule that binds biotin (claim 7) wherein the molecule that binds biotin is avidin, streptavidin or an anti-biotin antibody (claim 8) wherein the first nucleic acid is a PNA (claim 9) or an antisense PNA (claim 11) or bears a protecting group (claim 12) wherein the first nucleic acid comprises comprising a carboxyl terminal that is amidated (claim 10) wherein the first nucleic acid is a PNA having an amidated carboxyl terminal (claim 13) wherein the detectable label is selected from the group listed in claim 14 wherein said nucleic acid is labeled with a radiolabeled amino acid (claim 15) that is tyrosine labeled with  $^{125}\text{I}$  (claim 16) or lysine labeled with 111-indium (claim 17) wherein the gene is a gene that encodes a molecule selected from the group listed in claim 18 and the method of claim 1 wherein the first nucleic acid

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is a PNA, the targeting ligand is an antibody that specifically binds to a receptor on a cell of the blood brain barrier and the first nucleic acid is attached to the targeting ligand through an affinity tag (claim 19) wherein the antibody is monoclonal (claim 20), the imaging reagent comprises a radioactive or magnetic label (claim 21), the first nucleic acid is labeled with a radiolabeled amino acid (claim 22), the affinity tag comprises biotin (claim 23) and the antibody is monoclonal (claim 24) wherein the receptor is an insulin receptor (claim 25) and the method of claim 1 comprising systemic administration of the imaging reagent to a living organism (claim 28) wherein the organism is a mammal (claim 29) that is a non-human mammal (claim 30) or a human (31).

Penichet et al. disclose a method of in vivo systemic administration of an imaging reagent to rats (pg. 4424, col. 2 bridge 4425, col. 1) and detecting the quantity of a signal produced by the detectable label wherein the imaging reagent is [<sup>125</sup>I]anti-TfR IgG3-CH3-AvPNA, that comprises an antisense PNA that specifically hybridizes to a region of the *rev* mRNA of human immunodeficiency virus 1 (HIV-1) that comprises a targeting ligand that is an anti-transferrin monoclonal antibody linked to a the PNA by an affinity tag that comprises avidin and biotin wherein the carboxyl terminal of the PNA is amidated (pg 4423, col. 1) and the 5' terminal is biotinylated wherein the imaging reagent comprises a detectable label that is radiolabeled tyrosine [<sup>125</sup>I].

8. Claims 1-3, 6-16, 18-24, and 28-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Pardridge et al. 1995 (Reference 38, PTO-1449 filed 8/23/04, instant

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application). The invention as set forth in claims 1-3, 6-16, 18-24, and 28-30 is outlined in a previous rejection. Pardridge et al. disclose a method of in vivo systemic administration of an imaging reagent to rats and detecting the quantity of a signal produced by the detectable label (pg. 5593, col. 1) wherein the imaging reagent is [<sup>125</sup>I]-biotin-PNA/OX26-SA conjugate, that comprises an antisense PNA that specifically hybridizes to a region of the *rev* mRNA of human immunodeficiency virus 1 (HIV-1) that comprises a targeting ligand that is an anti-transferrin monoclonal antibody linked to a the PNA by an affinity tag that comprises streptavidin and biotin wherein the carboxyl terminal of the PNA is amidated (pg 4423, col. 1) and the 5' terminal is biotinylated wherein the imaging reagent comprises a detectable label that is radiolabeled tyrosine [<sup>125</sup>I].

### ***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

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under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-3, 5-25 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penichet et al. 1999 and Pardridge et al. 1995 as applied to claims 1-3, 6-16, 18-24, and 28-30 above, and further in view of Hnatowich 1999 (Reference 21, PTO-1449 filed 8/23/02, instant application), Kurihara et al. 1999 (Reference 27, PTO-1449 filed 8/23/02, instant application) and Tavitian (1998, Reference 48, PTO-1449 filed 8/23/02, instant application).

The teachings of Penichet et al. 1999 and Pardridge et al, 1995 and the invention as set forth in claims 1-3, 5-25 and 28-31 are outlined in a previous rejection (above).

Penichet et al. and Pardridge et al. do not teach a method of imaging in vivo expression of a gene in a brain cell in a vertebrate comprising a) administering an imaging reagent comprising a detectable label attached to a first nucleic acid that specifically hybridizes to a second nucleic acid transcribed from said gene where the first nucleic acid is linked to a targeting ligand that binds a receptor on a cell of the blood brain barrier and crosses said barrier and b) detecting the presence or quantity of a signal produced by the detectable label in brain cells wherein the presence or quantity of said label indicates the presence or quantity of a nucleic acid transcribed from said gene (claim 1) wherein the imaging reagent comprises a targeting ligand that is an

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antibody that specifically binds to an insulin receptor (claims 5 and 25), wherein said nucleic acid is labeled with a radiolabeled amino acid that is 111-indium or wherein said vertebrate is a human (claim 31).

Kurihara et al. teach the directed targeting of an EGF peptide radiopharmaceutical to image brain tumors in vivo wherein delivery is enabled to undergo transport thru the blood brain barrier (BBB) because of conjugation to a peptidomimetic MAb (monoclonal antibody) that transcytoses thru the BBB and the EGF peptide is radiolabeled with [<sup>111</sup>In]-labeled radionuclide chelated to EGF via a DTPA linker attached to lysine wherein the radiolabeled EGF is conjugated to a target delivery system via a biotin/streptavidin affinity groups (pg 6159, col. 1; pg. 6161, col. 2, 3<sup>rd</sup> paragraph). Kurihara et al. teach that their studies demonstrate that "peptide radiopharmaceuticals such as EFG can be used to image brain tumors when the molecules are conjugated to a BBB drug delivery system (pg 6162, column 2, 2<sup>nd</sup> paragraph) and that "Although the OX26 MAb is specific for rats, similar studies can also be performed in humans using BBB transport vectors that bind to human BBB receptors. A MAb to the human insulin receptor is active in humans and Old World primates, such as the Rhesus monkey, and has a BBB transport coefficient 9-fold greater than that found with anti-TfR MAbs. In addition to neuroimaging brain tumors, the use of a BBB drug delivery system and a peptide pharmaceutical could also be directed toward therapy of human brain tumors" (pg. 6163, col. 1) and that "Virtually any neurodiagnostic or neurotherapeutic agent can be conjugated to the BBB drug delivery system for non-invasive brain drug delivery in vivo" (pg. 6163, col. 1, last sentence).

Hnatowich 1999, in regards to antisense applications beyond chemotherapy teaches that "Antisense is also becoming useful as a research tool in molecular biology" (pg 693. col. 2, 2<sup>nd</sup> paragraph) and that "In the development of new radiopharmaceuticals, high specificity and high affinity of binding have always been recognized as useful properties. Accordingly, several potential applications of radiolabeled DNA as radiopharmaceuticals have been suggested. One nuclear medicine application, now obvious, involves the localization of radioactivity for imaging in tissues targeted by antisense mechanisms (i.e., antisense imaging) (pg 694, col. 1 bridge to col. 2) and that "To achieve therapy or imaging, antisense DNAs must cross the cell membrane and enter the cytoplasm" (pg. 696, col. 1, 4<sup>th</sup> paragraph) and that "It is hoped that the problem of poor cellular transport is soon resolved thereby removing perhaps the biggest hurdle to progress in antisense chemotherapy and, especially, to the development of antisense imaging (pg. 696, col. 2, 3<sup>rd</sup> paragraph) and that "Most radioisotopes used in nuclear medicine are metals. One straightforward approach to radiolabeling DNAs with metallic radionuclides is first to derivatize the antisense DNA on either of its ends with a primary amine, possibly attached by a suitable linker to minimize steric hindrance. The amine then may be conjugated with various metal bifunctional chelators such as anhydrides of diethylene-triamine pentaacetic acid (DTPA).... [S]ingle stranded DNAs have been radiolabeled in this manner with <sup>67</sup>Ga, <sup>111</sup>In and <sup>153</sup>Sm" (pg. 699 bottom of col. 2 bridge to pg 700, top of col. 1) and that "Clearly, antisense imaging would be an extremely valuable diagnostic tool, since, in

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theory, almost any tissue or disease state could be selectively imaged” (pg. 701, col. 2, 2<sup>nd</sup> paragraph).

Tavitian et al. teach that “Owing to their ability to block gene expression at the RNA level in vivo, antisense oligonucleotides are promising new pharmaceuticals” (pg. 467, col. 1, line 1) and that due to the need to chemically modify natural oligonucleotides to avoid rapid degradation and non-specific binding and to allow membrane passage, “[d]ozens of chemical alterations of the phosphodiester-deoxyribose backbone have been proposed, aimed at improving the pharmaceutical properties.... And that “Obviously, however, chemical modifications that modify sensitivity to nucleases, membrane passage, protein binding, etcetera, of the oligonucleotide should induce major alterations of its pharmacokinetics, whose knowledge is essential to evaluate its biological activity. Hence, a method allowing the measurement of the pharmacokinetics of oligonucleotides in vivo would offer significant progress I n evaluating the efficiency of strategies being developed to deliver oligonucleotides to target tissues for therapeutic purposes (pg. 467, col. 1, 2<sup>nd</sup> paragraph).

It would have been obvious to one of ordinary skill in the art to practice a method of imaging in vivo expression of a gene in a brain cell in a vertebrate comprising a) administering an imaging reagent comprising a detectable label attached to a first nucleic acid that specifically hybridizes to a second nucleic acid transcribed from said gene where the first nucleic acid is linked to a targeting ligand that binds a receptor on a cell of the blood brain barrier and crosses said barrier and b) detecting the presence or

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quantity of a signal produced by the detectable label in brain cells wherein the presence or quantity of said label indicates the presence or quantity of a nucleic acid transcribed from said gene) wherein said nucleic acid is an antisense peptide nucleic acid (PNA) that bears a protecting group wherein the targeting ligand is a monoclonal antibody that specifically binds to a receptor on a cell of the blood brain barrier and crosses said barrier wherein the first nucleic acid is linked to the targeting ligand by an affinity tag that comprises a biotin and an avidin (or streptavidin) wherein the PNA comprises a carboxyl terminal that is amidated wherein the detectable label is a radiolabeled amino acid that is tyrosine labeled with  $^{125}\text{I}$  wherein the gene encodes a structural protein wherein the method comprises systemic administration of the imaging reagent to a living organism that is a vertebrate, a mammal or a non-human mammal, as taught by Penichet et al. and Pardridge et al., wherein the imaging reagent is modified and comprises a targeting ligand that is an antibody that specifically binds to a human insulin receptor, as taught by Kurihara et al., and the nucleic acid is a PNA (which is considered a peptide pharmaceutical) labeled with a radiolabeled amino acid that is 111-indium attached to lysine via a DTPA linker as taught by Kurihara et al. and Hnatowich (now considered a peptide radiopharmaceutical or, at a minimum, a radiopharmaceutical), in order to image tissues targeted by antisense mechanisms, as taught by Hnatowich, and to measure the pharmacokinetics of oligonucleotides in vivo and evaluate their delivery as taught by Tavitian et al.

One of ordinary skill in the art would have been motivated to practice the method of the instant invention as taught by Penichet et al. and Pardridge et al., further

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comprising the limitations as taught by Kurihara et al. and Hnatowich because, as taught by Kurihara et al., "Virtually any neurodiagnostic or neurotherapeutic agent can be conjugated to the BBB drug delivery system for non-invasive brain drug delivery in vivo" (pg. 6163, col. 1, last sentence) and, as taught by Hnatowich, "Clearly, antisense imaging would be an extremely valuable diagnostic tool, since, in theory, almost any tissue or disease state could be selectively imaged" (pg. 701, col. 2, 2<sup>nd</sup> paragraph).

One of ordinary skill in the art would have expected success in practicing the method of the instant invention as taught by Penichet et al. and Pardridge et al., further comprising the limitations as taught by Kurihara et al. and Hnatowich because studies can be performed in humans using BBB transport vectors that bind to human BBB receptors using a MAb to the human insulin receptor that is active in humans and Old World primates, such as the Rhesus monkey, and has a BBB transport coefficient 9-fold greater than that found with anti-TfR MAbs and because "Virtually any neurodiagnostic or neurotherapeutic agent can be conjugated to the BBB drug delivery system for non-invasive brain drug delivery in vivo" (as taught by Kurihara et al.).

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

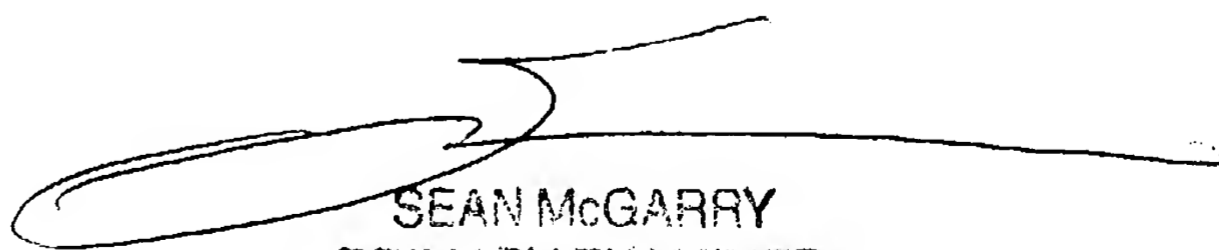
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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jba

  
SEAN MCGARRY  
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1635